Widespread synuclein pathology in hyposmics precedes dopamine transporter deficit in PARS

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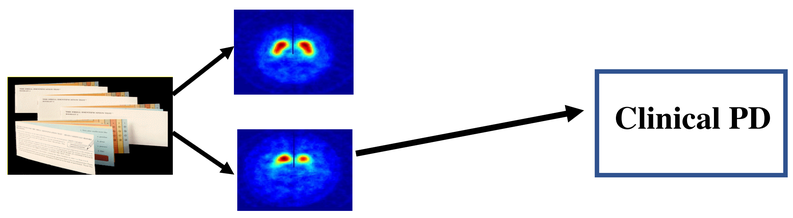
PARS

Introduction

The Parkinson Associated Risk Syndrome Study (PARS) is a longitudinal, observational study designed to investigate a sequential biomarker strategy using hyposmia followed by dopamine transporter (DAT) imaging to identify individuals from community populations at high risk of developing PD and related disorders. Data from PARS have shown that individuals with hyposmia are enriched for DAT deficit and in turn those individuals with hyposmia and DAT deficit are at high risk to develop a diagnosis of clinical PD .



We now report α-syn SAA data (in collaboration with Amprion). from the PARS study on the frequency of positive results with and without concurrent hyposmia. We further examine the temporal relationship between α-syn SAA status, DAT deficit and onset of clinical PD symptoms. We propose that a biomarker signature for PD can be detected that may enable screening and therapeutic interventions earlier in the pathological process at a point prior to onset of classical motor or cognitive symptoms.

PARS Cohort Ascertainment

PART 1 - Community ascertainment – remote data collection

N = 10,139 Returned screening and background questionnaire → **N = 4999 Completed UPSIT** → **N = 4330 Normosmic**; **N = 669 Hyposmic**

Hyposmia <15% by UPSIT

PART 2 - In clinic longitudinal clinical and biomarker data collection

N = 100 Normosmic; **N = 203 Hyposmic** — **CSF acquired during follow-up** → **N = 27 Normosmic**; **N = 73 Hyposmic**

CSF was acquired in 100 PARS participants, 27 normosmic and 73 hyposmic. Participants were followed for up to 10 years. Investigators were unaware of UPSIT or imaging data. In this analysis the PARS study visit at which CSF was obtained has been designated as a reference visit time 0.

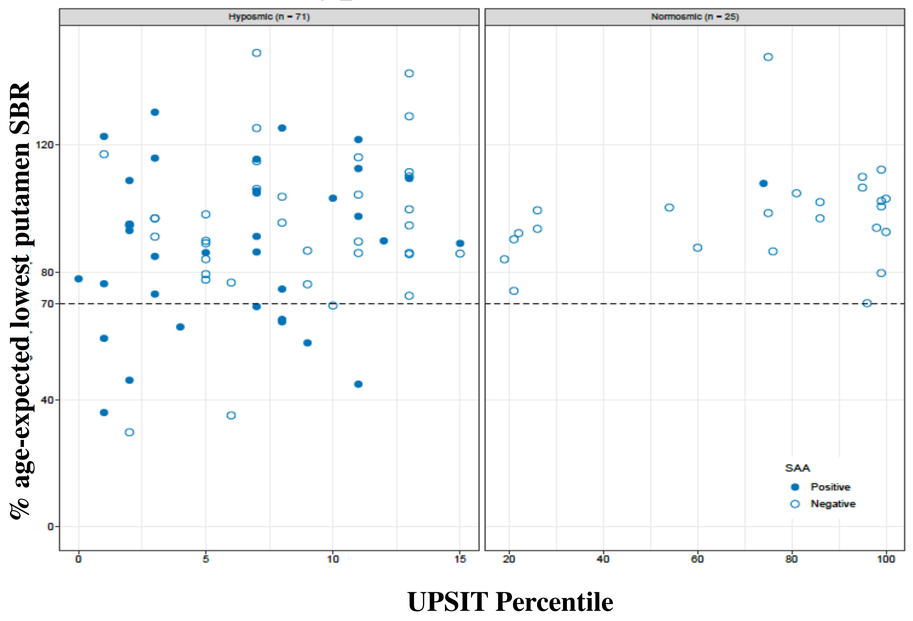
Comparison of PARS CSF cohort clinical and biomarker characteristics by olfactory and SAA status

Variable	Group: SAA+ Hyposmic* (N = 34)	SAA- Hyposmic (N = 37)	SAA- Normosmic (N = 24)	*p* value
Baseline clinical measures				
UPDRS part III score	1 (0, 3)	1 (0, 3)	0 (0, 2)	0.3231
MMSE total score	29 (28, 30)	29 (28, 30)	29 (28, 30)	0.8080
Missing	7	8	11	
RBD questionnaire total score	3 (2, 4)	1 (0, 3)	2 (0, 5)	0.2526
Missing	13	17	6	
Less than 1 bowel movement per day	7 (23%)	5 (15%)	3 (13%)	0.5440
Missing	4	3	1	
Baseline biomarker measures				
DAT lowest putamen SBR (% age-expected)	0.89 (0.69, 1.09)	0.95 (0.86, 1.06)	0.98 (0.89, 1.03)	0.4059
By category				0.0383
<70%	9 (26%)	3 (8%)	0 (0%)	
70-80%	4 (12%)	5 (14%)	3 (13%)	
>80%	21 (62%)	29 (78%)	21 (88%)	
Longitudinal clinical & biomarker outcomes				
Change in UPDRS part III score at 2-year visit	0 (0, 3)	0 (-1, 1)	0 (0, 4)	0.3815
Missing	4	4	16	
Change in UPDRS part III score at 4-year visit	2 (0, 8)	0 (-1, 0)	-	0.0003
Missing	14	19	-	
DAT < 70% at any visit	12 (35%)	4 (11%)	1 (4%)	0.0034
Clinical PD diagnosis	8 (24%)	0 (0%)	0 (0%)	0.0004

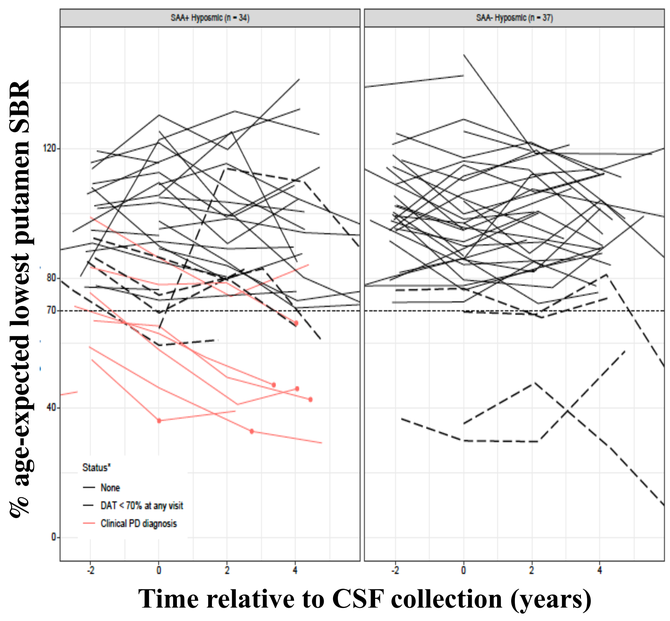
Data shown as median (IQR) or n (%).
Kruskal-Wallis tests were used to compare continuous measures; chi-square or Fisher's exact tests were used for categorical measures.
*One participant had CSF collected after completing all imaging visits; the last completed imaging visit was used to impute baseline measures.

α-syn SAA is positive in 47% of PARS hyposmics

SAA Status and DAT binding in PARS Hyposmics vs Normosmics



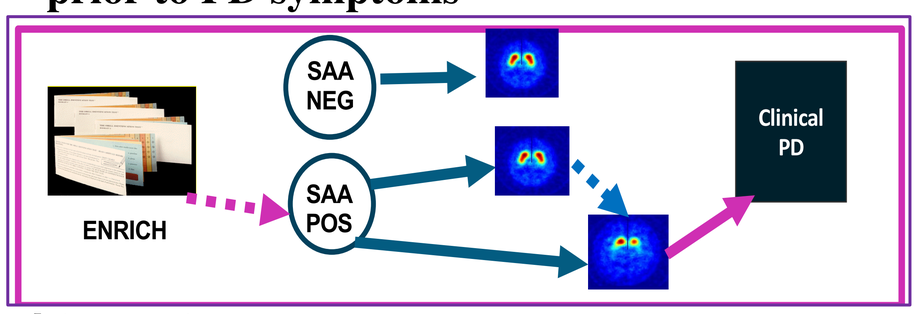
Longitudinal DAT in SAA Hyposmic Positive and Negative



Circles (o) refer to time of clinical PD diagnosis (if time of DAT imaging and clinical PD diagnosis overlapped). In the two remaining cases, the last imaging visit occurred 4 years prior to clinical diagnosis

- **Most SAA positive PARS participants have normal DAT at baseline.**
- **Most SAA positive PARS participants have normal DAT for at lease 4 years.**
- **Approx 30% of SAA+ PARS hyposmics compared to 8% of of SAA- PARS hyposmics show reduction of DAT at baseline and/or follow-up.**
- **Only PARS hyposmic SAA+ participants developed symptoms of NSD (8 of 12 DAT deficit). None of the SAA – hyposmics or normosmics developed symptoms. lowest putamen SBR**

Proposed Model for PD Biomarker Signature prior to PD symptoms



These data suggest:

- **in a community population > 60 years, ~7.5% are asyn SAA+**
- **hyposmia enriches for synuclein pathology**
- **there is a temporal progression to DAT deficit and clinical PD is some individuals**

Conclusions

- **These PARS data suggest that olfactory function testing may be a simple and easily accessible tool to identify α-syn SAA positive individuals before DAT imaging abnormalities or symptoms of PD occur.**
- **Further the proposed PD biomarker signature provides a new roadmap for therapeutic development to prevent or slow disease onset and will enable further studies to elucidate molecular disease subsets and ultimately more precise therapeutic targets based on disease biology.**

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